Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor
(Canagliflozin and Dapagliflozin)
Criteria for Use
VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

Exclusion Criteria

- ❑ Type 1 diabetes
- ❑ History of a serious hypersensitivity reaction to canagliflozin
- ❑ Estimated GFR (eGFR) < 45ml/min/1.73m^2 (for canagliflozin) and < 60ml/min/1.73m^2 (for dapagliflozin)
- ❑ On dialysis
- ❑ Pregnant or nursing
- ❑ Active bladder cancer or prior history of bladder cancer (for dapagliflozin)

Inclusion Criteria[1]

Monotherapy (must meet both criteria)

- ❑ Candidate for oral therapy and is intolerant of or has contraindications to use of metformin, sulfonylureas, pioglitazone, and DPP-4 inhibitors
- ❑ Expected change in hemoglobin A1c (A1C) is < 1% in order to reach patient specific goal[2]

Add-on therapy as part of an oral 2 drug regimen (must meet all 3 criteria)

- ❑ Inadequate glycemic control on monotherapy with metformin (at maximally tolerated dose) or sulfonylurea (at 50% maximal dose or highest tolerated dose), or pioglitazone (at maximally tolerated dose), or DPP-4 inhibitor
- ❑ Unable to tolerate or has contraindications to addition of a 2nd agent from the above mentioned group
- ❑ Expected change in A1C is < 1% in order to reach patient specific goal[2]

Add-on therapy as part of an oral 3-drug regimen (must meet all 4 criteria)

- ❑ Inadequate glycemic control on combination therapy with any 2 of the following drugs: sulfonylurea, metformin, pioglitazone, and DPP-4 inhibitor
- ❑ Unable to tolerate or has contraindications to addition of a 3rd agent from the above mentioned group
- ❑ Patient is not a good candidate for addition of insulin (e.g., Type 2 diabetics with special circumstances where the risk of severe hypoglycemia and/or its potential consequences are significant and/or catastrophic [e.g. frail elderly, liver failure, workers with frequent rotating shifts and occupations such as truck or bus drivers or heavy machinery operators] or patients who are unable to master injection technique)

  OR

  Patient declines insulin despite receiving information on pertinent therapeutic options and on his/her target A1c goal as well as on the ability of the various therapeutic options to achieve the desired A1c target goal and/or meet other clinical needs. Counseling should involve the patient's primary care provider(s) and, when feasible, instruction about and demonstration of insulin injection by those with expertise in diabetes care (e.g., diabetes educators, nurses, or other appropriate clinicians).
- ❑ Expected change in A1C is < 1% in order to reach patient specific goal [2]

Use with insulin

Consider discontinuing SGLT2 inhibitor if insulin is initiated.

1. Insulin may be considered at any time prior to using canagliflozin; however, it should be considered if patient is symptomatic or a greater reduction beyond what is achievable by canagliflozin is desired.
2. Refer to the Va/DoD Diabetes Guidelines **http://www.healthquality.va.gov/index.asp** for recommendations on individualizing A1C targets

Dosage

Refer to product labeling for dosing information

Please note the following:

- Dosing considerations for canagliflozin in patients with renal impairment
- Dosing considerations for canagliflozin for patients taking a UDP-Glucuronosyl Transferase (UGT) enzyme inducer (e.g., rifampin, phenytoin, phenobarbital, ritonavir)
- When used with a sulfonylurea or insulin, a lower dose of the sulfonylurea or insulin may be required as hypoglycemia was reported more often in those treated with this combination.
- Use of canagliflozin or dapagliflozin in patients with severe hepatic impairment has not been studied it is recommended that these agents not be used in these patients

Issues for Consideration

Hypotension: Canagliflozin and dapagliflozin cause intravascular volume contraction. Symptomatic hypotension may occur after initiation of the SGLT2 inhibitor particularly in patients with eGFR <60mL/min/1.73m^2, elderly patients, those taking diuretics. Labeling for canagliflozin also states increased risk for those taking medications that interfere with the renin-angiotensin-aldosterone system (e.g., ACEI, ARBs) or patients with low systolic blood pressure, orthostatic hypotension or autonomic neuropathy. Volume status should be assessed and corrected before initiating canagliflozin in patients with these characteristics. Monitor for signs and symptoms after initiating therapy. The dose of concomitant diuretics may need to be reduced.

Impairment in renal function: Canagliflozin and dapagliflozin can increase serum creatinine and decrease eGFR. Elderly patients, those with impaired renal function or hypovolemia may be more susceptible to these changes. Periodic monitoring of renal function is recommended. For canagliflozin, more frequent monitoring is recommended in patients with eGFR <60mL/min/1.73m^2.

Hyperkalemia: Hyperkalemia may occur with canagliflozin. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion (e.g., potassium-sparing diuretics, ACEI, ARBs) are more likely to develop hyperkalemia. Monitor serum potassium periodically in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Genital mycotic infections: Canagliflozin and dapagliflozin increase the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. For canagliflozin, uncircumcised males were at a higher risk for developing genital mycotic infections.

Hypersensitivity reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with canagliflozin and dapagliflozin. If hypersensitivity reactions occur, discontinue canagliflozin or dapagliflozin and treat per standard of care. If the reaction was serious, canagliflozin/dapagliflozin should not be restarted (see contraindications).

Increase in low-density lipoprotein (LDL-C): Dose-related increases in LDL-C occur with canagliflozin and dapagliflozin. Monitor LDL-C and treat per standard of care.

Pregnancy Category C: In rat studies, canagliflozin and dapagliflozin may affect renal development and maturation. The timing of these effects corresponds to 2nd and 3rd trimester of human development; therefore consider alternate therapy during pregnancy especially during the 2nd and 3rd trimester.

Lactation: Canagliflozin and dapagliflozin are secreted in milk of lactating rats. It is not known if canagliflozin or dapagliflozin is excreted in human milk. Data in juvenile rats showed risk to the developing kidney during maturation. In humans, kidney maturation occurs *in utero* and in the first 2 years of life. Because of the potential for serious adverse reactions to the nursing infant, a decision should be made to discontinue canagliflozin/dapagliflozin or nursing taking into account the importance of the drug to the mother.

Urinary Tract Infections: There is a slightly increased risk of urinary tract infections in patients receiving canagliflozin or dapagliflozin. It is unknown if use of canagliflozin or dapagliflozin poses additional risk in patients with a history of frequent UTIs, those with indwelling catheters, or need for self-catheterization or increased post void residual secondary to bladder outlet obstruction (e,g., BPH) or incomplete bladder emptying. Therefore, it is suggested that alternate therapy for diabetes be considered.

The efficacy and safety of an oral 4-drug regimen is not known and should be strongly discouraged. Such a trial might rarely be considered in patients with inadequate glycemic control on 3 drug therapy and who would not be a good candidate for the addition of insulin.
Discontinuation criteria
Discontinue if little to no improvement in glycemic (e.g., A1C, postprandial glucose) goals are seen after 3-6 months of therapy

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